'Targeting care: tailoring non-surgical management according to clinical presentation'

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Important points and objectives for recall:

- Numerous studies have explored patient characteristics including: body mass index, psychological factors, muscle strength, tibiofemoral alignment, radiographic changes and signs of inflammation as potential predictors of response to non-surgical interventions for management of hip and knee OA.
- Often the sample sizes utilized by these studies were inadequate to yield sufficient numbers of responders to the interventions to allow for analysis of the potential predictors identified.
- A number of well-designed studies were adequately powered to provide some evidence for clinical characteristics that did or did not predict response to non-surgical interventions for participants with hip and knee OA.

Synopsis

International evidence- based guidelines recommend a multitude of non-surgical treatment options for the management of OA. In the face of so many choices, it would be helpful for clinicians to be able to base treatment decisions on the identification of specific clinical presentations that foretell greater likelihood of success following a given treatment. This review summarizes the evidence available for patient characteristics that have been analysed as potential predictors of response to non-surgical interventions for patients with hip and knee OA. The specific variables targeted for this review include: body mass index, psychological factors, muscle strength, tibiofemoral alignment, radiographic changes and signs of inflammation. Several studies provide moderate to good evidence of potential predictors of response to non-surgical treatments, while areas for future research are illuminated.

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Introduction

The activity limitation attributed to osteoarthritis (OA) places it within the world's top 10 most disabling conditions (1). Globally OA affects approximately 18.0% of women and 9.6% of men over 60 years of age (2). In 2003 the annual costs of OA and other rheumatic conditions was an estimated $128 billion to the United States economy (3). These enormous costs are projected to rise steeply with the steadily increasing prevalence of rheumatic conditions (3).

This prevalent, expensive, disabling disease is incurable so it follows that current treatments focus on symptomatic relief. Commonly reported treatment goals for this group include reductions in joint pain, stiffness, activity limitation, participation restriction, and improvements in quality of life and well-being. To assist clinicians in achieving these goals with their patients, numerous international evidence-based guidelines for management of hip and knee OA have become available (4-10). There is uniformity in most of the recommendations made by the guidelines (11) and agreement that conservative management of hip and knee OA should combine both non- pharmacological and pharmacological treatment modalities (4-10).

The recommendations made in the guidelines for management of hip and knee OA are broad. The evidence-based, expert consensus guidelines from the Osteoarthritis Research Society International (OARSI) (2008) include no fewer than 20 recommendations for the non-surgical management of hip and knee OA (4), however the treatments are not arranged systematically to indicate the order of priority in which they should be undertaken. With so many recommended management options tabled, it would be advantageous to know which treatments are most likely to be effective for the individual with hip or knee OA according to clinical presentation.

This review examines the evidence available for identification of clinical characteristics which predict patient response to nonsurgical treatments for hip and knee OA. The summation of this evidence may assist clinicians to target treatments most likely to benefit patients according to clinical presentation, and identify areas for further research

Body Mass Index

Obesity is a known risk factor for development of arthritis (12) and is a strong predictor for long-term progression of the disease (13). There is evidence that obesity is a risk factor for knee OA however the relationship between obesity and the risk of developing hip OA is less clear (14, 15). International guidelines nonetheless recommend weight reduction in people with hip and knee OA who are overweight or obese (8, 9, 11, 16). There is strong evidence that weight loss is an effective treatment for knee OA, yet little evidence exists regarding weight loss as an effective treatment for obese patients with hip OA.

It seems reasonable that BMI may be a clinical characteristic that is predictive of response to weight loss interventions, surprisingly evidence exists that it does not. A post hoc analysis of an RCT involving 111 overweight veterans with knee OA, investigated nine clinical characteristics as possible predictors of weight change between baseline, 16 and 32 weeks. The minimum amount of weight loss required to define treatment responder was not provided. Multi-regression analysis revealed that BMI was not predictive of weight loss in response to the interventions for overweight veterans with knee OA (17). The external validity of this study is limited by confining recruitment of participants to veterans.

Two studies found that BMI was not predictive of response to a Dutch multi-modal, stepped care model of pain management for hip and knee OA. Snijders and colleagues (2011) investigated the efficacy of the Dutch model in a cohort of 183 participants with hip and knee OA (18). The model combined pharmacological and non-pharmacological treatments. Two possible definitions of positive treatment response were described: (i) Outcome Measures in Rheumatoid Arthritis Clinical Trials/ Osteoarthritis Research Society International (OMERACT-OARSI) Responder Criteria and (ii) patient reported numeric rating scale (NRS) for pain ≤ 4. At 12 week reassessment, 86 patients were responders according to definition (i), and 71 fulfilled definition (ii). BMI was one of eleven potential predictors of response included in analyses, and was not a significant predictor of response to this program (18), however the study was underpowered to identify true predictors of response. A more recent study utilized the same Dutch model, focussing specifically on a stepped-care protocol used to progress the use of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) at standardised intervals according to patient-reported pain levels (19). The definition of treatment responder was patient

reported NRS pain ≤ 4, 100 participants met this target. The study was underpowered to analyse 13 patient characteristics, including BMI, as possible predictors of response. Further research is required to determine whether BMI is predictive of positive treatment response achieved by participants of this multi-modal stepped-care model of pain management.

Two well-powered studies were identified examining the potential of BMI as a predictor of response to Cyco-Oxygenase-2 (COX-2) inhibitors. Bingham et al (2011) pooled the results of two similar RCT's comparing the efficacy of Etoricoxib and Celecoxib to placebo (20). The OMERACT-OARSI Responder Criteria determined that 562 participants were responders to the COX-2 inhibitors following 12 weeks of the intervention. BMI was one of 16 variables analysed as potential predictors of response, BMI failed to predict positive treatment response to the COX-2 inhibitors (20). Similar results were found by Detora et al (2001) combining the results of three 6 week RCT's comparing the COX-2 inhibitor Rofecoxib with placebo in 1501 patients with hip and knee OA (21). Responder criteria were not defined. Patient data was analysed according to subgroups representing 14 baseline characteristics including BMI. Analysis of covariance failed to identify any baseline measures associated with treatment response (21). To date good evidence exists that baseline BMI does not predict response of patients with hip and knee OA treated with COX-2 inhibitors.

A single study explored BMI as a predictor of response to intra articular corticosteroid (CSI) for management of hip OA. Robinson et al (2007) followed 120 patients with hip OA for 12 weeks following CSI (22). Participants were classified as responders to the CSI at 12 weeks if >15% reduction in baseline WOMAC pain sub-scale was achieved, 48 participants met this criteria. Logistic regression determined that BMI, one of 14 variables analysed, was not a significant predictor of response to hip CSI (22) however the study was underpowered to detect true predictors of treatment response.

Four cohort studies were identified exploring possible predictors of response to intra articular (IA) hyaluronic acid derivatives for hip and knee OA. Short term efficacy and tolerability of IA Hylan G-F 20 were assessed in 4253 patients with symptomatic knee OA.(23). Responder criteria were not defined, the primary outcome was pain measured at baseline and 3 weeks on a 4-point likert scale. At three week post IA Hylan G-F20 88.4% of patients assessed their pain as better or much better. Logistic regression of 7 potential predictors of short-

term pain reduction determined that underweight patients were more likely to report reduced knee pain than their obese counterparts. The method of recruitment threatens the validity of this evidence; the authors invited 840 orthopaedic surgeons to who report on at least five consecutive patients receiving Hylan G-F 20 for relief of Knee OA pain, introducing significant selection bias.

Longer term outcomes of patients with knee OA receiving IA Hylan G-F were explored in the following three cohort studies (24-26). A retrospective cohort of 155 patients with knee OA was reassessed 7-14 months following IA Hylan G-F 20 (24). The definition of responder was not specified. Analysis of 16 possible predictors found that BMI was not a significant predictor of patient satisfaction, though this study was underpowered to identify the possible predictors, and the retrospective design prone to significant recall bias. Longer term outcomes of Hylan G-F 20 were also studied in a small cohort of 32 patients with mild to moderate knee OA 6 months following IA Hylan G-F 20 (25). Clinical response was defined using the OMERACT-OARSI "high improvement" criteria, only 15 participants were responders, and 8 variables, including BMI, were investigated as predictors of response, leaving the study underpowered to detect significant predictors. BMI was not significantly correlated to patient response. A prospective cohort study examining 84 patients with knee OA for 6 months following knee IA Hylan G-F20 found that Short Form -36 health survey scores for were significantly improved at 6 months post injections (26). The responder criteria were not described. Three factors including the subjects' percentage above ideal body weight were analysed for correlations with positive treatment outcomes seen on the Short Form-36 health survey: Physical Function, Role-Physical and Role-Emotional categories. The subjects' percentage above ideal body weight was not predictive of improvements. The high number of patients lost to follow up (23%) affected the validity of this study. Evidence for BMI and % above ideal bodyweight as clinical characteristics predictive of longer term response to knee IA Hylan G-F20 was inconclusive due to low validity and power.

BMI was not a significant predictor of response of people with hip OA to IA Hylan G-F20. Migliore et al (2008) evaluated 250 patients with hip OA who received intra articular Hylan G-F20 (27). Treatment response was defined as a ≥30% improvement in baseline Lequesne scores or NSAID usage at 6 months, the number of participants classified as responders was unclear. Ten possible predictors of treatment response were

analysed, BMI was not a significant predictor of response to hip IA Hylan G-F 20 (27). The large number of drop-outs (42%) affected the validity of this study.

Patients with a lower BMI may be more likely to experience a reduction in chronic knee pain following treatment with glucosamine sulphate. A prospective correlational study of 39 participants with chronic knee pain followed patients receiving 1.5g daily glucosamine sulphate for 12 weeks (28). Participants were not required to have been diagnosed specifically with OA, affecting the external validity of this study. The definition of treatment responder was not described and 7 patient characteristics were examined to as potential predictors of reduction of pain rated on a VAS. The study was underpowered to determine effects of 7 potential predictors.

To date most of the evidence suggests that BMI is not a consistent predictor of response to non-surgical treatments for people with hip and knee OA. Some evidence exists that BMI is not predictive of response to a weight loss program in overweight veterans with knee OA (17). There is good evidence that BMI does not predict response to COX-2 inhibitors for hip and knee OA management (20, 21). The evidence is weak that BMI is not predictive of treatment response to either a multi-modal stepped-care pain management model (18, 19), hip CSI (22) hip IA Hylan G-F20 (27), or glucosamine for chronic knee pain (28). The evidence for BMI as a predictor of response to knee IA Hylan G-F is weak and conflicting (23-26). Further research is required to determine whether BMI is a clinical characteristic that can foretell response to non-surgical treatments for people with hip and knee OA.

Psychological factors

Complex interactions exist between psychological factors and perceived symptoms of OA. Compared with their peers, people with OA report increased prevalence of depression and depressed mood (29). The intensity of perceived OA pain has been demonstrated to be predictive of depression severity in this cohort (29). Poor mental health has been associated with worse overall hip and knee OA pain and deterioration in mental health has been found to precede short term exacerbations of OA pain (30). Treatment of depression in people with arthritis appears to improve depressive symptoms, reduce OA pain, improve function and quality of life (31) and therefore is an important consideration in the management of OA.

Many treatments prescribed for hip and knee OA management, particularly exercise, weight loss programs and medications; require active participation from the patient. The compliance with and efficacy of these treatments may be influenced by the individual's mental state to affect rehabilitation outcomes. The prospective cohort study "Predictors for response to rehabilitation in patients with hip or knee OA" (32) featured 250 patients with hip and knee OA who participated in a 3- 4 week multimodal rehabilitation program combining exercise therapy, hydrotherapy, relaxation strategies, distraction techniques, patient education, manual therapy, thermotherapy, and electrotherapy. Participants were assessed at baseline and 6 months following the program. Three different definitions of treatment responder were used: (i) the minimal clinically important difference (MCID) (18%) improvement shown on the WOMAC, (ii) improvement on the Transition scale, and (iii) MCID improvement on WOMAC and improvement on the Transition scale. The transition scale was described as a measure of the current state of health of the OA joint compared with its state 6 months earlier (32). There were 21 personal, lifestyle and psychological measures investigated as potential predictors of the three definitions of responder. Depression and anxiety were evaluated using the Hospital Anxiety and Depression Scale, mental health was assessed using the mental component of the SF-36. The absence of depressive symptoms was determined to be a strong predictor of all three of the responder definitions suggesting that depression may hinder the achievement of positive treatment outcomes of patients with hip and knee OA following a 3-4 week rehabilitation program. This study did not attempt to answer the question as to why they did not achieve the same results as their non-depressed counterparts, but we could hypothesize that perhaps those patients with depression have more difficulty complying with a comprehensive rehabilitation program. This is an interesting area for further research (32).

The presence of depression may affect the ability of overweight people with OA to lose weight. A post hoc analysis of an RCT aimed to identify predictors of positive treatment response resulting from weight loss interventions for 111 overweight veterans with knee OA (17). Veterans were randomized into groups receiving 24 weeks of nutritional counselling, a home exercise program, a combination of both or usual care. There were no differences in weight loss between intervention groups and 9 variables were investigated as possible predictors of weight change between baseline, 16 and 32 weeks of the RCT. The amount of weight loss required to indicate successful treatment response was not indicated. Symptoms of depression were

evaluated using The Centre for Epidemiologic Studies Depression Scale which measured 20 items to achieve a score out of 60. The presence of depression was indicated by a score ≥ 16. The absence of depression was the only independent predictor of weight loss at 16 weeks and 32 weeks (17). This study is limited by failure to define treatment responder; however it does suggest that depressive symptoms may limit the ability of veterans to lose weight.

Depression and anxiety did not seem to predict treatment response of patients with knee OA to CSI. A small study of 59 patients with knee OA receiving CSI examined 10 possible predictors of a favourable response, defined as a ≥ 15% reduction of pain rated on VAS, to injection of methyl prednisolone acetate(33). The Hospital Anxiety and Depression score at baseline was not found to consistently predict treatment response. Given that 59 patients were used to investigate 10 predictors of response, this study was underpowered to detect meaningful effects of the potential predictors.

Mental health scores do not seem to predict response to a combined non- pharmacological and pharmacological pain management program. Predictors for response to analgesics were explored in relation to a cohort study of 347 patients investigating treatment outcomes of a stepped model of care for hip and knee OA. The model initially offered education, lifestyle and weight loss advice, physiotherapy, acetaminophen, then progressed to other medications at intervals as guided by a pain numerical rating score (19). Treatment response was defined as achievement of pain NRS ≥4, there were 100 responders. Thirteen possible predictors of response were explored including mental health. The Short Form-36 (SF-36) questionnaire was used to assess health related quality of life and the mental component summary (MCS) scores of the SF-36 were used to reflect mental health. Mental health rated by the MCS was not a significant predictor of response to the stepped model of pharmacological pain management for patients with hip and knee OA, however this study was underpowered to analyse 13 possible predictors.

Self-reported participant mood failed to predict treatment outcome in a small cross- over RCT of 11 patients with osteoarthritis receiving two different NSAIDs (34). During two treatment periods of four weeks duration participants received ketoprofen and piroxicam. A 4 week wash-out period followed the initial drug treatment prior to commencement of the second drug. Participants were classified as treatment responders if they

showed ≥30% improvement of 5 of the 7 variables measured at baseline including; pain, tenderness, swelling, patient and physician global assessments, acute-phase protein levels and disability. There were 20 baseline variables explored as possible predictors of response including mood, assessed using an 18-item questionnaire. Mood was not a significant predictor of treatment outcome; however the small sample size of this study leaves it underpowered to detect meaningful effects of the predictors investigated.

In summary, two well-designed, adequately powered studies used specific measures of depression that were predictive of response to intervention (17, 32). Both studies demonstrated the relationship between the absence of depressive symptoms and positive non- pharmacologic treatment outcomes. The treatments investigated in these studies included a comprehensive rehabilitation program and weight loss interventions. These treatment modalities require high levels of active participation of the patients involved, which may be affected by the presence of depressive symptoms. Interestingly, the three studies investigating drug therapy regimes, perhaps not requiring such a high level of active participation by the subjects, consistently found different measures of psychological factors incapable of predicting treatment response (19, 33, 34). Two of these studies were underpowered (33, 34), and the third that was inadequately powered did not measure depression specifically.

Muscle Strength

In view of the biomechanical influence and protective functions of skeletal muscles surrounding joints, muscle weakness is considered to be an important possible factor in the development and progression of OA. Evidence for the significance of muscle strength in the pathogenesis of OA remains unclear (35, 36). Higher quadriceps strength may have a protective effect against the development of symptomatic OA (36). Whether muscle weakness precedes the onset of OA, or if it is a feature of already established disease seen on X-ray, or is only related to the onset of pain and other symptoms, is an area for further research.

The evidence for the role of muscle strength in the progression of OA is varied. Limited evidence exists to support muscle strength as a predictor of knee OA progression (13). Yet, over time, people with knee OA who have greater quadriceps strength report less pain and superior functional ability compared to their weaker counterparts (37). Quadriceps strength has been studied widely in relation to knee OA, however muscles

around the hip stabilising the pelvis also have an effect on adduction forces around the knee that may result in increased compression of the medial compartment (38) and influence the pathogenesis and progression of OA. Hip OA has also been associated with significantly reduced lower limb muscle strength (39), however limited evidence is available to explain the role of hip and thigh musculature in the development and progression of the disease. Further research is required to explain this possible relationship.

Treatments for hip and knee OA have long included specific exercises designed to strengthen muscles surrounding the joints involved. High level evidence exists regarding the reduction of pain and dysfunction in knee OA through therapeutic exercises (40). The evidence for the efficacy of exercise in hip OA to date is less convincing (41) yet exercise is often prescribed. Wright et al (2011) published a study aiming to identify baseline characteristics of patients with hip OA likely to respond favourably to Physical Therapy interventions (42). As part of a larger RCT, 91 patients were randomised to groups receiving manual therapy, exercise therapy, a combination of both or usual care. The OMERACT-OARSI responder criteria determined treatment responders. Ten variables were analysed as predictors of treatment response. Measures of muscle strength using a hand- held dynamometer were not predictive of treatment success. Only 22 of the 68 participants were responders which left the study underpowered to identify predictors of response (42).

There has been recent interest in the nature of lower limb muscle weakness in people with knee OA. Decreased quadriceps strength in knee OA has been attributed to both loss of muscle cross-sectional area (43) and reduced ability to activate the muscles (44). In a cohort of 111 subjects taken from a larger RCT, baseline ability to activate quadriceps was examined as one of 9 possible predictors of changes in strength of the muscle following a 6 week exercise program for subjects with knee OA. Primary outcome measures were quadriceps strength and quadriceps activation, measured using a burst-superimposition maximum isometric quadriceps torque test, however a definition of treatment response was not identified. Although lower quadriceps activation was associated with lower strength, the baseline quadriceps activation did not predict the magnitude of gain in quadriceps strength following exercise therapy (45). These results suggest that patients with OA should benefit from strengthening exercises regardless of baseline quadriceps activation.

Baseline muscle strength does not seem to predict the degree of symptomatic relief achieved following a weight loss program in obese people with knee OA. The 192 participants, who were part of larger RCT, were randomised to two different dietary interventions. Significant response to the interventions included the OMERACT-OARSI responder criteria and improvement on KOOs scores. Although weight loss was achieved in most of the subjects, only 64% achieved the OMERACT- OARSI responder criterion. There were 23 variables investigated as possible predictors of response to the weight loss programs, including measurements of baseline hamstrings and quadriceps strength using isometric dynamometry. Baseline muscle strength was not predictive of symptomatic relief in response to the weight loss program (46). The study was underpowered to detect significant predictors from a possible 23 variables.

One study investigated muscle strength as a predictor of response to a pharmacological agent. Jones et al (1996) performed a cross-over RCT comparing CSI with saline (placebo) in 59 subjects with knee OA (33). Ten possible predictors of treatment response were analysed. Treatment response defined as ≥ 15% decrease in pain rated on a visual analogue scale, was not predicted by baseline quadriceps strength measured using a commercial strain gauge. This study was significantly underpowered to analyse 10 predictors of response.

Further research into the role of muscle strength in the pathogenesis of OA and subsequent progression of the disease may be helpful in refining recommendations for therapies aimed at OA prevention and further joint deterioration as a consequence of OA. To date, muscle strength has not been demonstrated to predict response to non-surgical interventions for hip and knee OA

Tibiofemoral Joint Alignment

Varus (bow-legged) or valgus (knock-kneed) tibiofemoral joint alignments are clinical characteristics observed in some people with knee OA. Joint alignment impacts the distribution of load borne by the medial and lateral compartments of the articular surface of the knee. Static knee alignment is conventionally determined using full- length weight bearing radiographs of the lower limb with knees extended. Lines are drawn from the centre of the femoral head to the talus through the middle of the femoral and tibial shafts to indicate the loadbearing mechanical axis, then measurements made of various angles subtended from where those lines intersect (47-49). Neutral alignment is commonly defined as 0-2 degrees of varus (50) meaning that in a

normal knee the mechanical axis passes medial to the knee joint resulting in 60-70% of weight bearing forces to pass through the medial articular surface (51). Varus malalignment results in higher loads borne through the medial compartment of the knee, whereas increased compressive forces through the lateral articular surface accompany valgus malalignment.

Dynamic knee alignment can be assessed using 3-D gait analysis. In varus knees the measurement of knee adduction moment during stance phase of walking is an indirect measure of joint compressive forces sustained within the medial tibiofemoral joint compartment (49, 52, 53). Static and dynamic alignment are important to consider in view that altered distribution of forces placed through the joint surface may lead to damage of articular structures, possibly increasing risk of OA development or worsening existent disease.

It remains unclear whether knee joint malalignment precedes incident knee OA (47, 48), however varus alignment considered to be a significant predictor of knee OA disease progression (13). Knee malalignment has been demonstrated to interact with other risk factors for OA progression, increasing the likelihood of disease acceleration. Possible interactive factors include greater quadriceps strength (54), the stage of disease observed in the individual (55) and obesity (48).

The evidence for the relationship between knee malalignment and reported OA symptoms remains unclear (55, 56). Nevertheless, some non-surgical treatments in OA management guidelines aim to reduce pain and dysfunction associated with tibiofemoral malalignment. Orthotic bracing, shoe wedges and muscle strengthening are recommended with a view to improve biomechanics of the joint (4, 6, 7, 9, 10). Several studies have investigated knee joint alignment as a predictor response to non-surgical management of OA. An RCT by Lim et al (2008) examined the effect of a 12 week quadriceps strengthening program on knee adduction moment, pain, and function in 107 subjects with knee OA. Knee alignment was assessed on radiographs and participants stratified according to whether they had more neutral (< 5 degrees) or more varus (≥5 degrees) alignment. Specific responder criteria were not described. Patients in the strengthening group achieved significant improvements in strength regardless of alignment. Self-reported function, performance measures and knee adduction moment determined using 3-D gait analysis were unchanged by the intervention in both alignment groups. Pain, assessed using the WOMAC pain subscale, was significantly

improved in the strengthening group subset that was more neutrally aligned. Neutral knee joint alignment may mediate improvements in knee OA pain following a 12 week quadriceps strengthening program (57).

Immediate changes in static alignment and knee adduction moment were not predictive of response to lateral wedge insoles at 3 months. A cohort of forty volunteers with knee OA were provided with laterally wedged insoles to assess the immediate effects of the insoles on knee OA pain, knee adduction moment and static alignment (49). The lateral wedges immediately reduced knee adduction moment calculated using 3-D gait analysis and walking pain measured using the WOMAC pain subscale, but had no effect on static alignment as determined on full length leg radiographs. Alignment was defined as the angle subtended by the intersection of the femoral and tibial mechanical axes. Varus malalignment was determined when the angle was <180 degrees with valgus indicated by >180 degrees. After 3 months of wearing the insoles, significant improvements in pain and function persisted. A definition of treatment responder was not explained; nevertheless 10 predictors at baseline of outcome to intervention at 3 months were explored. Neither immediate changes in static alignment or knee adduction moment were predictive of decreased pain and improvement in function 3 months following the intervention (49). The size of this cohort limited the ability of this study to identify true predictors of response to the intervention.

A larger RCT of 192 obese subjects with knee OA allocated patients to two different weight loss interventions (46). Knee joint alignment was assessed using a 'Plug-in Gait model' with a six camera stereophotogrammetric system and markers on anatomic landmarks. A knee was categorised as varus when alignment was > 0 degrees, and valgus if < 0 degrees. Baseline knee alignment was one of 23 variables examined as possible predictors, however it failed to predict improvements in Knee Injury and Osteoarthritis Outcome Scores (KOOS) or achievement of OMERACT- OARSI Responder Criterion following weight loss interventions (46). In view that only 64% of patients were treatment responders according to OMERACT-OARSI criterion, the study was underpowered to detect effects of significant predictors.

It is interesting to consider the definitions of knee malalignment utilised in the three studies discussed above. Lim et al (2007) employed a more extreme definition of ≥5 degrees to indicate varus malalignment (57). In contrast the two other studies categorized subjects to knee malalignment groups if the mechanical axis did not

appear as a straight line (46, 49). This may have increased the severity of malalignment observed within the participants assigned to the varus group investigated by Lim and colleagues, compared to the subjects categorized to knee malalignment groups in the other studies. Participants with varus malalignment studied by Lim et al (2007) did not experience improvements in pain following strength-training, while the neutrally aligned reported significant pain reduction (57). Perhaps the higher severity of varus malalignment was key to the determination of knee joint alignment as a predictor of outcome to intervention in this study. Future research considering knee malalignment as a predictor of treatment response to conservative treatments should consider carefully the definition of joint alignment.

Radiographic and MRI Assessment

The presence of radiographic osteophytes (OP) and joint space narrowing are commonly used to diagnose OA. These features are combined to determine radiographic disease severity according to scoring systems such as the Kellgen-Lawrence grade (KLG) (58). Despite known limitations, radiographs are inexpensive, accessible and easy to interpret, so are commonly used in research for classification of subjects to determine eligibility and for stratification of samples according to radiographic severity. Radiographic joint space width (JSW) or minimum joint space width (mJSW) is recommended for use in clinical trials, however MRI is preferred particularly for assessment of cartilage morphology (59).

Relatively few papers analyse radiographic severity of hip and knee OA as possible predictors of response to non-surgical, non-pharmacological treatments. Two of the three papers identified doing so examined the ability of radiological and MRI OA severity to predict response to weight loss interventions. A small RCT of 30 obese female participants with knee OA compared two dietary weight loss interventions (60). Within the intervention group 90% of participants achieved clinically significant weight reduction of >10%, and 33% had a 50% improvement in knee OA symptoms. A strict definition of treatment responder was not provided. Structural joint damage was assessed at baseline using both the KLG classification, and low field MRI (0.2T) to assess various measures of cartilage abnormalities, bone marrow lesions (BML's) effusions and synovitis of the medial, lateral and patellofemoral compartments of the knee. Five baseline radiographic characteristics and clinical outcomes following the weight loss interventions were investigated for correlations. None of the

imaging variables were able to forecast symptomatic response to treatment (60) however this study was likely underpowered to identify significant predictors.

A second RCT randomized 192 obese patients with knee OA into 8 weeks of two experimental dietary interventions (46). Results were calculated for the entire cohort as the method of weight loss was not relevant for this analysis. OA symptoms were evaluated at baseline and 16 weeks using the OMERACT- OARSI Responder Criteria and changes in KOOS. High field MRI was assessed using the Boston-Leeds Osteoarthritis of the Knee Score (BLOKS) to measure joint damage at baseline. Conventional radiography determined the baseline KLG and minimum Joint Space Width (mJSW). MRI and radiographic measures failed to find any relationship between variables assessing knee structural damage and symptomatic improvements following the dietary interventions (46). Only 64% of patients were treatment responders according to OMERACT-OARSI criterion, therefore this study may also be insufficiently powered to detect effects of 23 potential predictors.

A third study examining the ability of radiographic features to predict response to non-surgical, non-pharmacological interventions was conducted by Hinman et al (2008) (49). A cohort of 40 patients with knee OA wore full length 5 degree lateral wedge insoles for 3 months. Improvements were observed in WOMAC pain and function subscales following the intervention. Tibiofemoral OA severity was assessed at baseline using the KLG scoring system. Following analysis of 10 possible predictors of outcome, greater disease severity indicated by higher KLG scores were predictive of worse pain at 3 months. This study does not define responder criteria, and the small sample size reduced the ability to identify predictors of response to lateral wedge insoles.

Two studies examine radiographic severity using KLG as potentially predictive of response to interventions combining both non-pharmacological and drug therapies for hip and knee OA. Both investigated cohorts of patients with hip and knee OA participating in a Dutch multi-modal, stepped-care pain management program (18, 19). During the 12 week program subjects received standardised non-pharmacological management and pain relieving medications prescribed and altered at set intervals depending on self-reported pain at reassessment. The definition of positive treatment response in the initial cohort of 183 patients was fulfilment of either the OMERACT-OARSI Responder Criteria or NRS ≤ 4 (18). The later study of 347 subjects required NRS

≤ 4 at 12 weeks to indicate successful response to the intervention (19). Both studies analysed OA severity as determined by KLG scores as possible predictors of positive treatment outcomes. The first study tested 11 possible predictors of response to intervention and found that disease severity did not forecast improvements in overall pain and function as a result of the 12 week pain management program. (18). In the second study, 13 predictors were tested for correlation with treatment response at the 4 different steps of the treatment model. Greater OA severity was independently associated with a higher chance of pain relief achieved in response to use of acetaminophen (19). This correlation was discovered because unlike the first study, the predictors of response were tested at each of the separate steps of the program. There were 59 responders to Acetaminophen, so the study was underpowered to test 13 predictors. Although the evidence is tenuous, this finding lends support to the recommendations made by international OA management guidelines to trial acetaminophen as a first line pharmacological treatment of hip and knee OA (4-10), even in those patients with severe disease.

Evidence to the contrary was presented by Case et al (2003) in the results from a double blind, placebo-controlled RCT comparing the efficacy of acetaminophen and diclofenac sodium for pain management of knee OA (61). Eight-two patients were randomized to 3 groups receiving either one of the drugs or placebo. The primary outcome at baseline, 2 and 12 weeks was the WOMAC scale. The diclofenac sodium group alone achieved significant improvement (≥20%) in all 3 WOMAC subscales following the intervention. The subjects were stratified according to pre-study medication, baseline pain and disease severity indicated by KLG, in order to identify subsets of patients that were consistent in response to the treatments. None of the sub-groups consistently demonstrated preferential response to acetaminophen or diclofenac sodium. This study suffered from a high number of dropouts (>25%). Three of the five subjects who withdrew from the diclofenac sodium treatment arm (n=25) did so as a result of adverse effects. Despite the evidence presented in this paper for the superior efficacy of diclofenac sodium, the relatively high risk of unwanted side effects lends further weight to the OA treatment guidelines recommending a trial of acetaminophen prior to commencing NSAID therapy (4-10) and it can be presumed that this follows regardless of radiographic severity.

Four articles were identified investigating radiological predictors of response to CSI for hip OA. Of these, only one reported that radiographically determined disease severity was a significant predictor of positive response

to steroid injection (62). This retrospective cohort study reviewed radiographs, radiology reports and medical records of 361 patients who had received fluoroscopically guided IA 80 mg depo medrol or methylprednisolone with bupivocaine. The definition of treatment responder was a 50% decrease in pain reported on a Visual Analogue scale (VAS). Immediate positive response to injection was evident in 68.2% of hips and delayed response was apparent in 71.4%. OA severity was measured at baseline using KLG classification and the grades were split into groups for analysis. Multivariate regression determined that radiographic severity of OA was an independent predictor of treatment response. Patients with advanced disease were much more likely to experience both immediate and delayed onset of pain relief. The authors suggested that people with advanced hip OA are likely to achieve better response to CSI than those with mild or moderate disease (62). Although a good number of participants were recruited, these inferences should be considered cautiously in view of the inherent risk of bias associated with the retrospective cohort design of this study.

In contrast, Robinson et al (2007) utilizing a similar fluoroscopically guided injection of methylprednisolone and bupivacaine into the hip joint of a 120 people with hip OA concluded that radiographically determined OA severity was not predictive of response to intervention (22). This cohort study assessed symptomatic response to 40 mg and 80mg dosages of the steroid. A decrease in the WOMAC pain by >15% was considered to indicate positive treatment response, 75 patients were classified as responders at 6 weeks. The authors concluded that the higher dose (80mg) of methylprednisolone was more effective and lasted longer. Twelve possible predictors of treatment response included KLG scoring. Forward logistic regression found that KLG was incapable of predicting reduced pain in response to hip CSI (22). This study was underpowered to detect predictors of response among 12 variables.

Similar conclusions were made regarding a small prospective cohort of 27 patients with hip OA assessed at baseline, 2, 12 and 26 weeks following hip IA lignocaine and methylprednisolone (63). The main outcome measure was pain measured on VAS. The degree of radiological severity according to KLG classification and mJSW had no significant bearing on the reported pain relief following hip steroid injection however the small sample size decreased the power to detect significant predictors. The fourth RCT compared ultrasound-guided CSI to IA hyaluronic acid, saline (control), and standard care (no injection) in 77 subjects with hip OA (64).

Response to treatment was delineated by the OMERACT-OARSI Responder Criteria, there were 14 responders to steroid injection. CSI was significantly more effective than the 3 other treatments. Univariate regression analysis determined that of 5 predictors analysed, radiographic severity using Croft grading and mJSW were not predictive of treatment response to CSI however the study was underpowered to analyse 5 predictors (64). Further research is required to explore the value of radiographic and MRI clinical characteristics indicating disease severity as potential predictors of response to hip CSI.

Three cohort studies attempted to identify radiographic characteristics of patients with hip and knee OA that were predictive of treatment response to IA Hylan G-F 20(24, 25, 27). Migliore et al (2008) followed 250 patients who received US-guided IA hylan G-F 20 into OA hips (27). Treatment response was defined as improvement of ≥30% Lequesne index or NSAID use. Significant improvements were reported for all outcome measures at 3,6, 9 and 12 months when compared to baseline. Multiregression analysis of 8 baseline variables determined that KLG was unable to predict treatment response (27). A high number of drop outs limited the validity of this study. The second study followed a small cohort of 32 patients with mild to moderate knee OA for 6 months following knee IA Hylan G-F 20 (25). The OMERACT-OARSI "High improvement" responder criteria for OA were utilized to define responders to treatment. Fifteen participants met the responder criteria. Eight predictors of treatment response were explored, including mJSW which was not predictive of positive response to Hylan G-F 20 injection (25). The study was underpowered and limited by the exclusion of patients with severe OA. Conrozier et al (2003) (24) studied a cohort of 155 patients across the spectrum of mild through to severe knee OA. Knee joint space loss in a single compartment seen on radiograph and meniscal calcinosis noted on MRI scans were predictive of good outcome to knee IA Hylan GF-20. The definition of treatment responder was not adequately described in this retrospective cohort, so it is difficult to define the improvement that is actually predicted by these measures (24).Nevertheless, weak evidence exists that knee joint space loss in a single compartment and meniscal calcinosis may predict response to IA Hylan G-F 20, and this warrants further research.

Bennett et al (2007) (28) investigated symptomatic response of 39 subjects with chronic knee pain treated with 1.5g oral Glucosamine sulphate for 12 weeks. Primary outcome measures at baseline and 3 months included pain VAS rated on movement, VAS for restriction in function and patient-rated global change score.

These outcomes were all found to be significantly improved at 12 weeks but the responder criteria were not specified. Seven possible predictors of reduced pain and improved functional ability were analysed using regression modelling. The authors concluded that lower levels of PFJ osteophytes, BMI and functional self-efficacy, were predictors of successful glucosamine treatment. The presence of osteophytes within the medial and lateral compartments of the tibiofemoral joint was not correlated with response to the intervention (28).The study was underpowered to identify true predictors of response and participants did not require formal diagnosis of OA, so these results must be viewed accordingly.

Overall, there was weak evidence that radiographic measures of OA severity may have predictive value in identification of potential responders to lateral wedged insoles (49), CSI (62) and glucosamine sulphate. MRI assessment was predictive of response in a single study concerned with knee Hylan G-F 20 injections (24). A greater number of studies exist that were unable to predict response to treatment based on radiographic disease severity or MRI. There is good evidence that KLG scores are not predictive of response to hip CSI (22). Further research is required to clarify the roles radiography and MRI perform as clinical characteristics that predict response to non-surgical treatment for hip and knee OA.

Inflammation

Abnormal progressive remodelling of joint tissues occurs in response to local inflammatory processes arising within osteoarthritic joints (65). Physical examination may reveal clinical signs such as presence of joint swelling, effusion and heat. With recent improvements in imaging techniques, synovial hypertrophy has become a surrogate marker of local inflammation within a joint.

Signs of inflammation were examined as potential predictors of response to weight loss interventions for participants with knee OA. The clinical cohort described by Gudbergsen et al (2012) participated in a 4 month dietary intervention (46). Responders were required to fulfil the OMERACT-OARSI responder criteria. Joint damage severity was assessed on MRI using the Boston-Leeds Osteoarthrits Knee Score (BLOKS) which included scoring for synovitis and effusion. Although synovitis and effusion were not predictive of OMERACT-OARSI response, there was some evidence that the effusion score correlated with changes in the KOOS ADL score from baseline to 4 months. Responder criteria for the KOOS score were not provided. There were 23

variables assessed as potential predictors of response, 123 patients were responders, therefore this study was insufficiently powered for this many predictors. The presence of inflammatory markers such as effusion and synovitis requires further investigation as predictors of symptomatic response to weight loss interventions for overweight patients with OA.

Systemic pharmacological agents such as NSAID's and COX-2 inhibitors are prescribed for their analgesic properties and also to reduce inflammatory activity in affected joints. Two studies found that the presence of swelling was not predictive of response to these drug therapies. The data of three 6 week RCT's comparing rofecoxib with placebo were combined to analyse the consistency of response of patients with hip or knee OA classified into subgroups determined by 14 demographic and disease factors (21). Three outcome measures were analysed in relation to the subgroups; Pain walking on flat surface (WOMAC), Patient Global Assessment of Response to Therapy, and Global Assessment of Disease Status. The definition of treatment responder was not provided. Overall, the subgroups did not show consistent interactive effects with all three outcome measures. The absence of knee swelling of participants with knee OA significantly correlated with improved scores on the Patient Global Assessment of Response to Therapy, but not the 2 remaining outcome measures (21). Another study investigated swelling among numerous possible predictors of response of patients with OA and rheumatoid arthritis to ketoprofen and piroxicam (34). The trial was very small with 11 participants with OA, so was underpowered to determine significant predictors of response (34). Further investigation into signs of inflammation as possible predictors of response to NSAID's and COX-2 inhibitors would be helpful to the clinician attempting to tailor pharmacological management according to clinical presentation.

Intra articular corticosteroids aim to directly reduce inflammatory processes occurring within joint tissues. An RCT by Chao et al (2010) examined inflammatory characteristics assessed on ultrasound (US) as predictors of response to intra articular corticosteroid injection for knee OA (66). Participants were categorised as 'inflammatory' if synovial hypertrophy (synovitis) with or without effusion was detected on grayscale US examination of the affected knee(s) at baseline. Within the intervention group 16 patients presented with synovitis on US, and 18 did not. At 4 weeks there were no significant differences between the inflammatory and non-inflammatory subgroups. Significantly lower WOMAC pain scores of the non-inflammatory sub-group at 12 weeks suggested that those without inflammatory characteristics experienced prolonged beneficial

effects from corticosteroids. The presence of effusion had no influence on response to corticosteroid injection (66).

The presence of hip joint synovitis on US assessment of patients with hip OA was predictive of treatment response to CSI. An RCT compared standard care (no injection), injection of normal saline (placebo), non-animal stabilised hyaluronic acid and methylprednisolone acetate (64). Of the participants receiving CSI, 14 participants were classified as responders according to the OMERACT-OARSI criteria. The authors concluded that synovitis was predictive of response at 4 and 8 weeks following injection, however this study was underpowered to establish clear associations between the 5 variables analysed as possible predictors. In contrast, Robinson et al (2007) found that evidence of hip synovitis and effusion on US were not predictive of clinical response to intra articular methylprednisolone injection (22). The cohort study defined response to intervention as >15% reduction in baseline WOMAC pain score at 6 and 12 weeks following injection. This study was also underpowered to identify predictors of response. Further research using greater numbers of subjects is required to explore US determined inflammatory characteristics as predictors of response to CSI of osteoarthritic hips.

Inflammatory characteristics identified on physical examination of patients with knee OA failed to predict response to CSI. The presence of local inflammation indicated by knee joint fluid, local heat, synovial thickening and stiffness were explored as possible predictors of response to intra articular methylprednisolone in an RCT of 59 participants with symptomatic knee OA (33). No predictors of response were identified, perhaps a result of this study being underpowered. Pendleton et al (2008) examined similar clinical signs of inflammation; presence of heat, effusion and synovial thickening in addition to the presence of effusion and synovitis on knee US, as predictors of improvements in baseline WOMAC pain scale 1 and 6 weeks following CSI (67). The presence of heat was associated with 29% greater reduction in night pain, otherwise clinical and US inflammatory signs were not predictive of response. The study was underpowered and did not publish any measures of data variability. Adequately powered well-designed research is necessary to determine whether clinical and US signs of inflammation are predictive of outcomes following CSI for knee OA.

Moderate effusion was associated with good outcome following intra articular injection with Hylan G-F 20 in patients with symptomatic OA. Conrozier et al (2003) followed a cohort of 155 patients who received three intra articular hylan G-F 20 injections and were evaluated 7-14 months later (24). Treatment outcomes included patient satisfaction, safety, changes in pain and function which were assessed on 4-point Likert scales. This study was limited by the lack of validated outcome measures and the retrospective study design.

Only one study investigated signs of inflammation as predictive of outcome to non-surgical, non-pharmacological intervention. There is weak evidence that that synovitis and effusion seen on MRI are unable to predict response to weight loss in patients with OA (46). Numerous studies were concerned with signs of inflammation as predictors of outcomes to pharmacological agents, but few were sufficiently powered. Some evidence exists that knee joint swelling may predict good outcomes from rofecoxib (21) and that patients without synovitis observed on US experience prolonged pain relief following CSI injection compared to those patients with knee OA presenting with synovitis (66). The evidence for synovitis on US as a predictor of response for outcomes following hip CSI is conflicting (22, 64). There is little evidence to support the use of clinical inflammatory signs as predictors of response to CSI for knee OA (33, 67) .Further research is required to determine whether signs of inflammation are useful predictors of response to conservative therapies for people with hip and knee OA.

Other clinical characteristics that may predict response to intervention

For the purposes of this review we have selected patient characteristics that we deemed interesting to examine as potential predictors of outcome to interventions for people with hip and knee OA. There is a wider range of presenting features than those covered here, analysed as potential predictors of response and further discussed in the literature. Among the articles identified through literature searches for our chosen predictors, age and gender were commonly analysed as potential predictors of response to intervention, but appeared to hold little predictive capacity overall. Four well-powered studies investigating predictors of response to; COX-2 inhibitors (20, 21), a rehabilitation program (32), and exercise therapy (45) provided moderate to good

evidence that age was not a powerful predictor of response to these interventions. Further investigation of age as a predictor of response to alternative interventions for patients with hip and knee OA is justified.

One adequately powered study determined female gender to be a characteristic predictive of treatment success following participation in a rehabilitation program (32). In contrast, three well-powered studies found gender not predictive of treatment success for COX-2 inhibitors and exercise therapy (20, 21, 45). Additional research into gender as a predictor of treatment response to different non-surgical modalities is required.

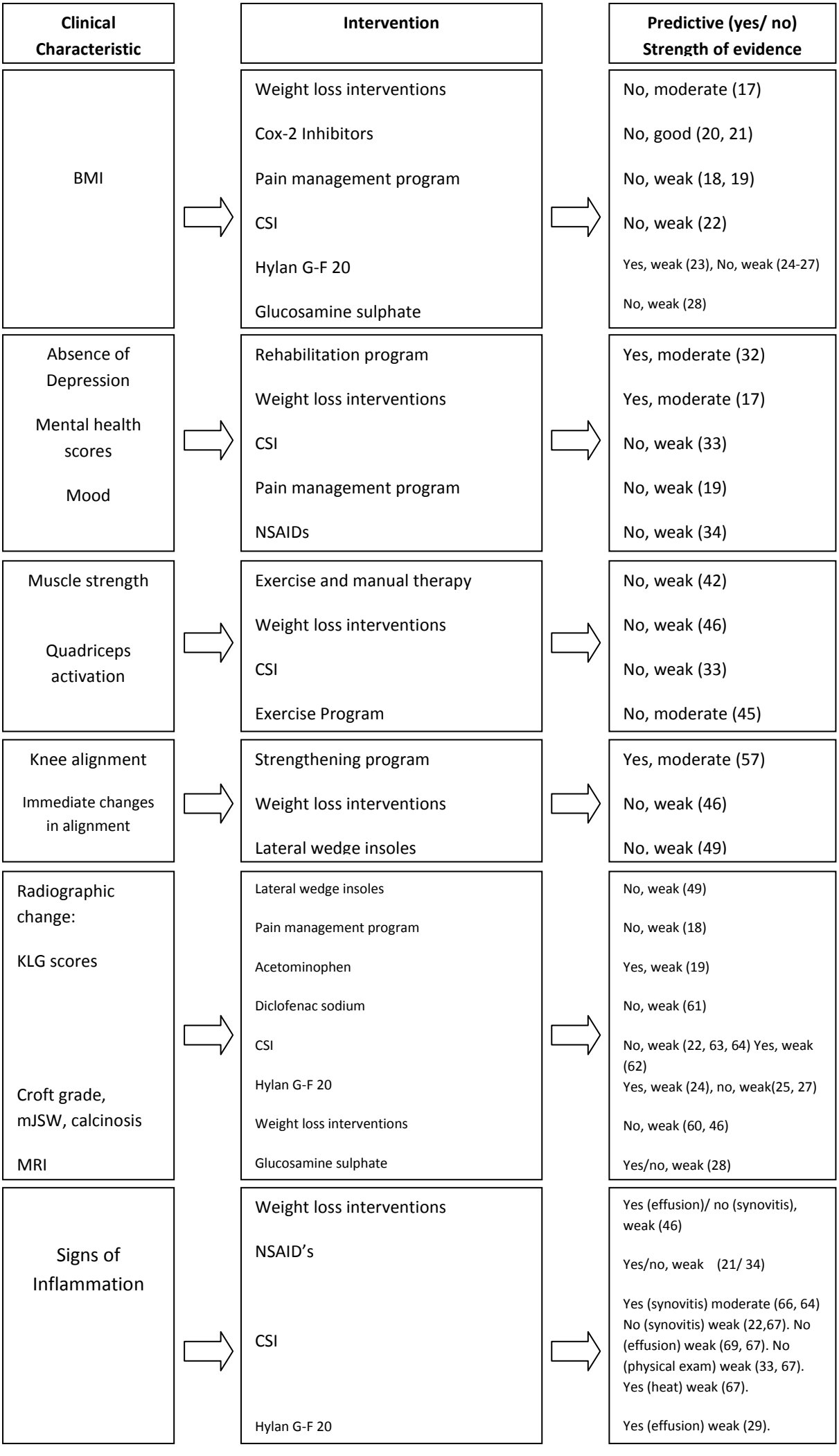
Pain and function WOMAC subscales are often used as primary outcome measures in OA research. Of the studies extracted from literature searches performed around our chosen predictors, two well-designed studies examined WOMAC pain and function scores as predictors of response to COX-2 inhibitors. One found that that baseline WOMAC pain was not predictive of response to Etoricoxib and Celecoxib. Lower levels of function on the WOMAC decreased the odds of response to the drugs, but the difference in WOMAC function scores between responders and non-responders was not clinically significant (20). The second study concluded that baseline WOMAC function was not predictive of response to Rofecoxib (21). Although baseline WOMAC pain and function scores were not predictive of response to COX-2 inhibitors, these measures may prove to be interesting predictors of response to different non-surgical interventions in other research.

Summary

This review identified and summarized the evidence available for particular features of clinical presentation exhibited by people with hip and knee OA that were predictive of response to non-surgical interventions. The studies are summarized in Figure 1. Good evidence exists that BMI is not predictive of response to COX-2 inhibitors for hip and knee OA (20), and moderate evidence presented that BMI does not predict weight reduction following weight loss interventions for overweight people with knee OA (68). There is some evidence to suggest that the absence of depressive symptoms predicts successful outcomes from both weight loss interventions in overweight people with knee OA (68) and a 3-4 week rehabilitation program for participants with hip and knee OA (32). Moderate evidence was sited that quadriceps muscle activation was not predictive of improvements in quadriceps strength attained by participants with knee OA during a strengthening program (45). Patients with medial knee OA who were neutrally aligned were more likely than

their more varus aligned counterparts to achieve significant pain relief following a quadriceps strengthening program (57). Evidence was lacking for any radiographic or MRI changes that were significant predictors of response to non-surgical interventions, however patients with knee OA presenting without inflammatory characteristics on US (synovitis) were more likely to experience prolonged benefit from CSI than inflammatory patients (66).

The practice of analysing patient characteristics as potential predictors of response to interventions is becoming increasingly popular. Researchers attempting to identify predictors of clinical response to non-surgical treatments for hip and knee OA require the use of larger sample sizes, or restriction of the number of variables analysed such that 10-15 responders are studied per possible predictor (69). Identification of further characteristics capable of predicting response to intervention would indeed provide clinicians with additional tools to tailor non-surgical care of patients with hip and knee OA according to their clinical presentation.


Clinical Characteristic
Intervention
Predictive (yes/ no) Strength of evidence
BMI
Weight loss interventions
Cox-2 Inhibitors
Pain management program
CSI
Hylan G-F 20
Glucosamine sulphate
No, moderate (17)
No, good (20, 21)
No, weak (18, 19)
No, weak (22)
Yes, weak (23), No, weak (24-27)
No, weak (28)
Absence of Depression
Mental health scores
Mood
Rehabilitation program
Weight loss interventions
CSI
Pain management program
NSAIDs
Yes, moderate (32)
Yes, moderate (17)
No, weak (33)
No, weak (19)
No, weak (34)
Muscle strength
Quadriceps activation
Exercise and manual therapy
Weight loss interventions
CSI
Exercise Program
No, weak (42)
No, weak (46)
No, weak (33)
No, moderate (45)
Knee alignment
Immediate changes in alignment
Strengthening program
Weight loss interventions
Lateral wedge insoles
Yes, moderate (57)
No, weak (46)
No, weak (49)
Radiographic change:
KLG scores
Croft grade, mJSW, calcinosis
MRI
Lateral wedge insoles
Pain management program
Acetominophen
Diclofenac sodium
CSI
Hylan G-F 20
Weight loss interventions
Glucosamine sulphate
No, weak (49)
No, weak (18)
Yes, weak (19)
No, weak (61)
No, weak (22, 63, 64) Yes, weak (62)
Yes, weak (24), no, weak(25, 27)
No, weak (60, 46)
Yes/no, weak (28)
Signs of Inflammation
Weight loss interventions
NSAID's
CSI
Hylan G-F 20
Yes (effusion)/ no (synovitis), weak (46)
Yes/no, weak (21/ 34)
Yes (synovitis) moderate (66, 64) No (synovitis) weak (22,67). No (effusion) weak (69, 67). No (physical exam) weak (33, 67). Yes (heat) weak (67).
Yes (effusion) weak (29).

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